UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,779	01/02/2001	Wei-ping Li	12013/55202	7468

26646 7590 05/20/2003

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/750,779	Applicant(s) Wei-Ping Li et al.
	Examiner Dave Nguyen	Art Unit 1632

-- *Th MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 6, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *61-66* is/are allowed.

6) ☒ Claim(s) *1, 4-6, 9, 10, 15, 19, 24, 28-33, 36-49, 59, and 60* is/are rejected.

7) ☒ Claim(s) *2, 3, 7, 8, 11-14, 16-18, 20-23, 25-27, 34, 35, and 50-58* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1, 6, 15, 33, 37, 38, 43, 46 have been amended, claims 47-66 have been added by the amendment filed March 6, 2003. The species restriction has been withdrawn by the examiner because of the amendment to the claims and because all presently pending claims are free of the prior art of record.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 10, 15, 19, 24, 28, 33, 38, and 43 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to the presently pending claims, drawn specifically to the agents as listed in claims 6, 15, 24, 33 and 43, the specification only provides sufficient description of anti-thrombogenic proteins (heparin, heparin derivatives, urokinase, and PPACK), antioxidant compounds (probucol and retinoic acid), angiogenic proteins, agents which block smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic/antiproliferative/anti-mitotic compounds, anti-microbial compounds, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoting proteins, vascular cell growth protein inhibitors, vascular cell growth antibody inhibitor, cholesterol lowering drugs, vasodilating drugs, proteins that protect against cell death, cell cycle CDK protein inhibitor, anti-restenosis proteins, agents for treating malignancies, bone morphogenic protein, and polynucleotides encoding any of the above named proteins. However, the claims as written embrace an enormous number of anti-thrombogenic agents other than anti-thrombogenic proteins, angiogenic agents other than angiogenic proteins, vascular cell growth promoting agents other than growth factors, vascular cell growth inhibitors other than antibodies or anti-growth factor proteins, agents other than proteins that protect against cell death, cell cycle inhibitors other than cell cycle CDK protein inhibitors,

anti-restenosis agents other than anti-restenosis proteins, and of polynucleotides encoding any of the agents as claimed including those compounds (small molecular weight compounds or drugs) that is not known by any prior art to be encoded by a polynucleotide.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or formula containing unspecified molecular structures of molecules that are essential for the making the genus of one or more negatively charged therapeutic agents as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of one or more negatively charged therapeutic agents which are employed in the context of implantation of therapeutic molecules by medical delivery devices that must exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to a formula containing no chemical structure but rather just functional effect of the drugs and/or DNA encoding "such agents" because the disclosure of no more than what were indicated on pages 9 and 10 of the specification, as in the instant case, is simply a wish to know the identity of any and/or all other agents and/or DNA having the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of other agents and/or DNA encoding "such agents" that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,

1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed and recited agents that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's response (pages 12-15) has been considered by the examiner but is not found persuasive because of the reasons set forth in the stated rejection. Applicant's citation of *Hoerschler* is not found persuasive because of the claims do claim specifically polynucleotides encoding agents that are not even construed by a skilled artisan to be polypeptides, and even if the agents are, neither the as-filed specification nor any of the prior art nor *Hoerschler* provides any evidentiary support to demonstrate that the written description of a representative number of species of agents as claimed have been met by the as-filed specification.

Claims 1, 6, 10, 15, 19, 24, 28, 33, 36, 38, and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A medical device as claimed in linking claims 1, 10, 15, 28 and 38, wherein at least one of the one or more negatively charged therapeutic agent comprises at least one agent selected from the group consisting of anti-thrombogenic proteins, antioxidant compounds, angiogenic proteins, agents which block smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic/antiproliferative/anti-mitotic compounds, anti-microbial compounds, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoting proteins, vascular cell growth protein inhibitors, vascular cell growth antibody inhibitor, cholesterol lowering drugs, vasodilating drugs, proteins that protect against cell death, cell cycle CDK protein inhibitor, anti-restenosis proteins, agents for treating malignancies, bone morphogenic protein, and polynucleotides encoding any of said proteins or protein inhibitors.

This rejection stands because of the reasons set forth in the written description rejection.

During the interview with applicant on May 15, 2003, applicant were receptive to a claim amendment to cancel the rejected claims. However, no active step has been made, and thus, the rejection is maintained for the reasons of record.

Claims 38-49, 59-61, readable on a gene therapy method for treating or reducing the occurrence or severity of a clinical disease or condition by an implantation of the claimed medical device at any location, *e.g., in vitro,* remain and/or are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A method delivering a therapeutic agent to a mammal, the method comprising implanting a medical device comprising the coating as recited in claim 28 at a desired location or tissue in a mammal, wherein the coating comprises a therapeutic agent;

A method delivering a DNA encoding a protein to a mammal, the method comprising implanting a medical device comprising the coating as recited in claim 38 at a desired location or tissue in a mammal, wherein the coating comprises a polynucleotide encoding a protein; and

A method delivering a DNA encoding a therapeutic protein to a mammal, the method comprising implanting a medical device comprising the coating as recited in claim 38 at a desired location or tissue in a mammal, wherein the coating comprises a polynucleotide encoding a protein selected from the group consisting of anti-thrombogenic proteins, angiogenic proteins, vascular cell growth promoting proteins, vascular cell growth protein inhibitors, proteins that protect against cell death, cell cycle CDK protein inhibitor, anti-restenosis proteins, and bone morphogenic protein.

The specification does not reasonably provide enablement for the presently pending claims encompassing any other combination of therapeutic agents and/or DNA encoding such agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of agents and/or polynucleotides encoding "such agents" for use in an implantable or insertable delivery device as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended.

In addition, the claims as written do not necessarily limit the "location" to a desired location or target tissue in a mammal. However, the specification only teaches that in order to employ the claimed medical device within applicant's framework of the invention, it is necessary to implant the claimed medical device to a desired target tissue in a mammal. As such, it is not apparent how one skilled in the art practices the full breadth of the claimed methods on the basis of applicant's disclosure.

With respect to claims readable on a method of gene therapy to treat or reduce the occurrence or severity of a clinical disease or condition in any animal, Applicant's claimed invention encompasses gene therapy products so as to prevent the occurrence of a disease or condition, or to produce a therapeutic effect in any subject having any disease by using a medical device comprising any therapeutic DNA including antisense, nucleic acids, and vectors comprising any therapeutic gene, including those that are yet to be discovered. The specification indicates that any disease including vascular diseases, non-vascular can be therapeutically treated by using the claimed method and/or pharmaceutical compositions.

Other than a sufficient enablement of direct administration of an anti-proliferative gene to inhibit restenosis or the growth of tumor cells in a mammal, and of a DNA coding for an angiogenic factor to induce the growth of blood vessels at a site of the local delivery of the DNA, as indicated in the specification and state of the prior art of record (Isner, US Pat No. 5,652,225, for example), it is not apparent as to how one skilled in the art determines, without undue experimentation, as to which of other DNA as embraced by the claims would exhibit a therapeutic effect in the treatment of a disorder, particularly on the basis of

applicant's disclosure, and given the unpredictability of nucleic acid therapy methods at the time the invention was made (Anderson *et al.,* Nature, Vol. 392, 25-30, April 1998). With respect to the use of DNA coding for antisense, ribozymes, triplex oligonucleotides, to treat a tissue *in vivo* therapeutically, the application does not demonstrate a therapeutic effect in any subject using any of the disclosed DNA as claimed. There is no evidence for an affect on any disease symptom using any of applicant's therapeutic nucleic acid. Major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the treatment in a treated subject (Anderson, Nature, Vol. 392, 25-30, April 1998; Rosenberg, Science, Vol. 287, page 1751, 2000). More specifically, Anderson teaches that results in one particular animal model have not always reflected what happens in another animal model (page 28, column 1, first paragraph), that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types. Verma *et al.* (Nature, Vol. 389, 18, September 1997, pages 239-242) also states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would

generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). With respect to antisense therapy, Branch (TIBS 23, pp. 45-50, 1998) even in 19998, antisense and ribozyme therapy remains unpredictable (entire document). The specification does not provide sufficient guidance and/or factual evidence demonstrating a reasonable correlation between the disclosure and the subject matter being sought in the claims. Thus, it is not apparent as to how one skilled in the art reasonably extrapolates, without any undue experimentation, from a therapeutic effect generated by direct injection of DNA coding for an angiogenic factor, as demonstrated in the prior art of record, to any and/or all pharmaceutical products as recited in the presently pending claims, particularly given the unpredictability of gene therapy and/or the doubts expressed in the art of record. Note that the essential attributes and/or criteria of the claimed DNA gene therapy compositions as claimed, *e.g.,* routes of administrations, dosages, and/or specific structures of antisense and/or ribozymes, and/or therapeutic DNA, that exhibit a therapeutic effect, are not sufficiently described in the as-filed specification so as to overcome the doubts expressed in the art of record. Note that the issue is not that the specification and the prior art of record does not reasonably provide an enablement of a method of using the claimed medical device to provide the proteins as disclosed and supported by the as-filed specification to any mammal, but is rather that at the time the invention was made, the use of the claimed medical device to treat or reduce the occurrence or severity of any clinical disease or condition in any animal is neither routine nor reasonably predictable at the time the invention was made. Thus, the specification is not enabling under 35 U.S.C. 112, first paragraph, for any and/or all therapeutic nucleic acid constructs within the context of treatment of any disease in any subject, particularly on the basis of applicant's disclosure and the reasons stated in the art of record.

Applicant asserts on pages 17-21 that the claimed invention is not solely directed to gene therapy *per se,* however, to the extent that the rejected claims embrace gene therapy, the issues of gene therapy are relevant and thus the rejection remains proper. Note that applicant's guidance as to applicant's contemplation of claim patentability of the full breadth of the claims does not necessarily mean that applicant's claims are reasonably enabling at the time the invention was made, under 35 USC 112, first

paragraph. Thus, applicant's citation of *In re Buchner, MPEP 2164.01, In re Marzocchi* are not found persuasive.

Applicant's citation of references that employ gene therapy protocols to treat various tumors, hemophilia, diabetes in animal models has been noted, however, the references do not cure the deficiency of the presently pending claims which claim that the claimed medical devices can be use to treat in preventing or reducing the occurrence of any clinical disease or condition in any animal including human subjects. Note that the fact that numerous Phase I clinical trials, which is drawn mainly to safety issues of tumor treatment, do not necessarily lend any evidence that applicant 's claims are fully enable at the time the invention was made.

Claims 2, 3, 7, 8, 11-14, 16-18, 20-23, 25-27, 34-35, 50-58 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER